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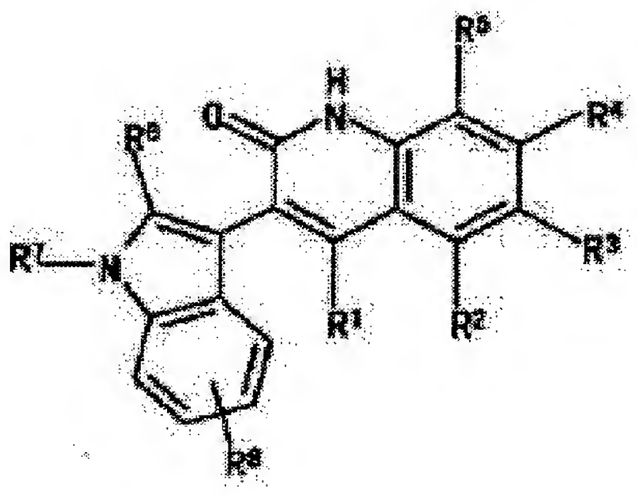
(54) CARBOSTYRYL COMPOUND AND ITS MEDICINAL USE

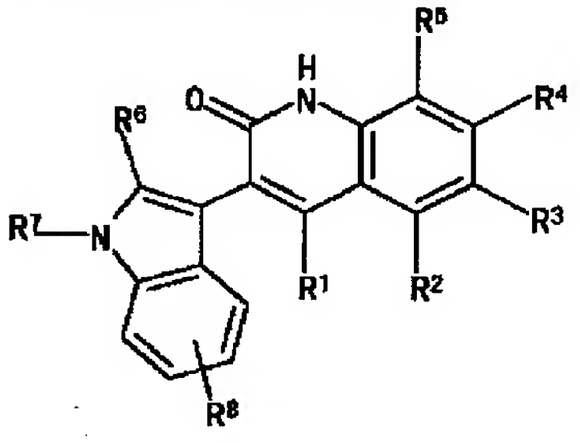
(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a compound and a phamaceutically acceptable salt thereof, useful as a smooth muscle growth inhibitor, therapeutic agent of restenosis and a therapeutic agent of nephritis by strongly inhibiting phosphorylation of PDGF receptor.
SOLUTION: This carbostyryl compound is represented by the general formula (1) (R1, R2, R3, R4 and R5 are each same or different group of a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, an amino group, a lower alkyl group, a lower alkoxy group or the like; R6 is a hydrogen atom or a halogen atom; R7 is a hydrogen atom, a lower alkyl group or the like; and R8 is a hydrogen atom, a halogen atom, a lower alkyl group, a hydroxy group, a carbox group, an amino group or the like).



(1)

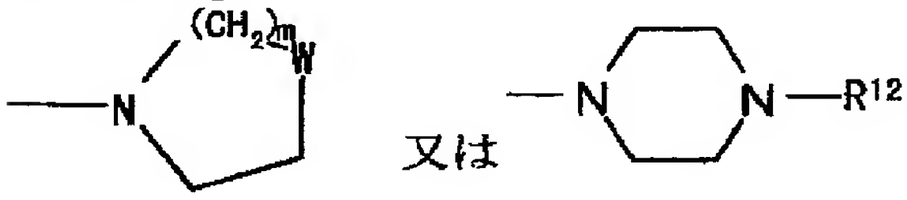
CLAIMS

[Claim(s)]
[Claim 1]A general formula (1)
[Chemical formula 1]

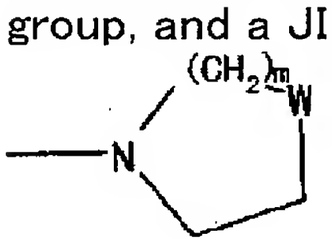


(1)

R^1, R^2, R^3, R^4, and R^5 are the same or different among [type -- hydrogen atom; halogen atom; -- low-grade -- low-grade alkyl-group; nitro group; replaced with an alkyl-group; halo alkyl-group; hydroxyl group
- The inside of a CO-A-R^9[type and R^9 are a hydrogen atom, a low-grade alkyl group, an aryl group, or -Alk-R^{10} (here). R^{10} An aryl group, an amino group, a lower alkylamino group, it is a JI lower alkylamino group, a carboxyl group, or a low-grade alkoxycarbonyl group, and Alk is alkanediyl or alkenediyl -- it is -- A -O- or -NR^{11}- (here) R^{11} should become together with a hydrogen atom, a low-grade alkyl group, or a nitrogen atom in which R^{11} and R^9 adjoin. [Chemical formula 2]

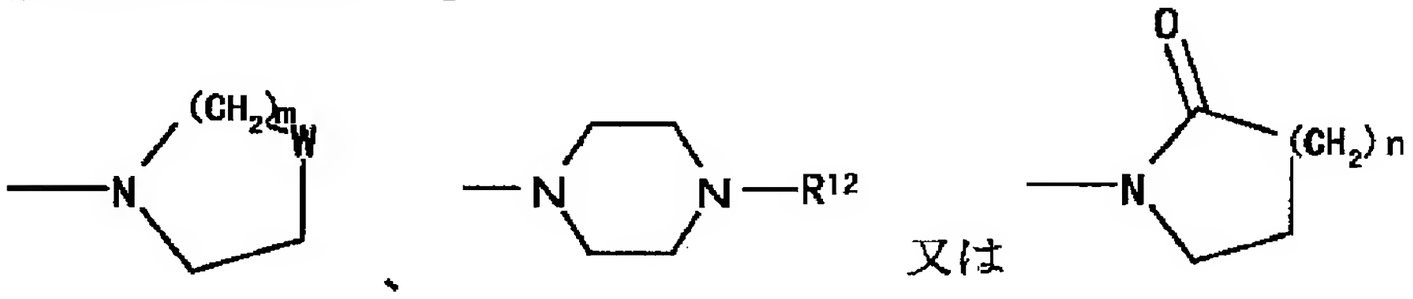


it may form (W is $-CH_2-$ or -O-, m is an integer of 1 thru/or 3 here, and R^{12} is a hydrogen atom, a low-grade alkyl group, an aryl group, or an aralkyl group) -- it is --];
R^{13} among an O-B-R^{13}[type -A hydrogen atom, A low-grade alkyl-group, low-grade alkenyl-group, and halo alkyl group, a cycloalkyl group, an aryl group (this aryl group -- a halogen atom of 1 thru/or 2, and a low-grade alkyl group.) it may be replaced by an amino alkyl group, a lower alkoxy group, or a cyano group which may be replaced by a low-grade alkyl group -- a heteroaryl group (this heteroaryl group -- a halogen atom of 1 thru/or 2, an amino group, a lower alkylamino group, and a JI lower alkylamino group -- or) [Chemical formula 3]

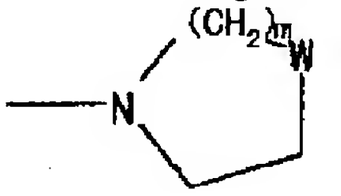


It may be replaced by (here, W and m are the same as the above), [Chemical formula 4]

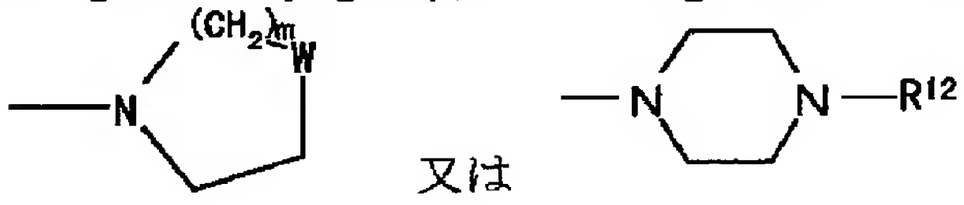
here -- R^{14} -- a hydrogen atom, a low-grade alkyl group, and an aralkyl group. It is a low-grade alkoxycarbonyl group or an aryl sulfonyl group (an aryl group of this aryl sulfonyl group may be replaced by halogen atom or a low-grade alkyl group), or is -Alk-R^{15} (here). Alk is the same as the above and R^{15} A halogen atom, a halo alkyl group, a cycloalkyl group and an aryl group (this aryl group -- a halogen atom of 1 thru/or 2.) A low-grade alkyl-group and halo alkyl group, an amino alkyl group which may be replaced by a low-grade alkyl group, . It may be replaced by trifluoromethyl group, hydroxyl group, lower alkoxy group, nitro group, lower alkylamino group, or a JI lower alkylamino group. A heteroaryl group, a hydroxyl group, a lower alkoxy group, a cycloalkoxy group, an aryloxy group or an aralkyloxy group, $-NR^{16}-R^{17}$ (here) R^{16} and R^{17} become together with a nitrogen atom in which it is the same or different, and a hydrogen atom, a low-grade alkyl group, a cycloalkyl group, an aryl group, an aralkyl group or R^{16}, and R^{17} adjoin, [Chemical formula 5]



. It may form (here, n is an integer of 1 thru/or 2 and W, R^{12}, and m of it are the same as that of the above). Low-grade alkyl carbonyl group, arylcarbonyl group, carboxyl group, low-grade alkoxycarbonyl group, and $-CO-NR^{18}-R^{19}$ (here) R^{18} and R^{19} be the same or different, and become together with a hydrogen atom, a low-grade alkyl group, or a nitrogen atom in which R^{18} and R^{19} adjoin. [Chemical formula 6]

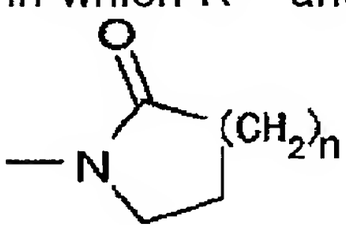


It may form (here, W and m are the same as the above), or certain B is -CO- and $-CO-NR^{20}$ at a low-grade alkyl sulfonyl group. - (here) R^{20} should become together with a hydrogen atom, a low-grade alkyl group, or a nitrogen atom in which R^{20} and R^{13} adjoin. [Chemical formula 7]



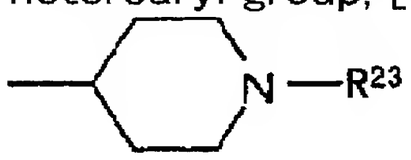
it may form (here, W, R^{12}, and m are the same as the above) --]; which is -CS-, $-CS-NR^{20}-$ (here, R^{20} is the same as the above), $-SO_2-$, or a single bond

- R^{21} should become together with a hydrogen atom, a low-grade alkyl group, or a nitrogen atom in which R^{21} and $-D-R^{22}$ adjoin among a $NR^{21}-D-R^{22}${type. [Chemical formula 8]

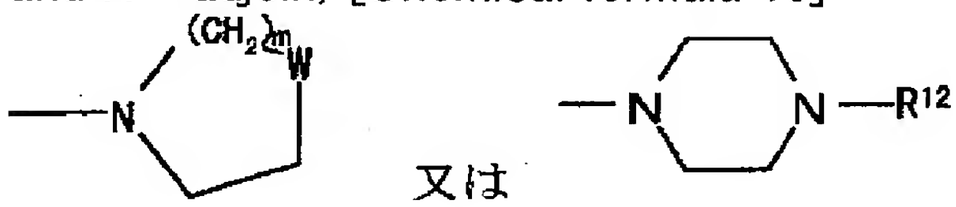


May form (here, n is the same as the above), and R^{22} A hydrogen atom, A low-grade alkyl-group, low-grade alkenyl-group, and halo alkyl group, a cycloalkyl group, An aryl group (this aryl group

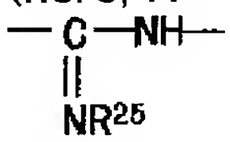
may be replaced by an amino alkyl group, a lower alkoxy group, or a cyano group which may be replaced by halogen atom of 1 thru/or 2, low-grade alkyl group, and a low-grade alkyl group), a heteroaryl group, [Chemical formula 9]



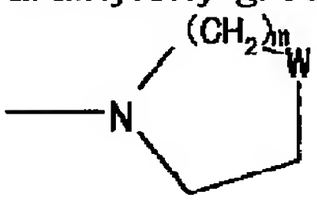
(Here, R^{23} is a hydrogen atom, a low-grade alkyl group, an aralkyl group, a low-grade alkoxycarbonyl group, or an aryl sulfonyl group (aryl of this aryl sulfonyl group).) it may be replaced by halogen atom or a low-grade alkyl group -- it is -- or -Alk-R^{15} (here) Alk and R^{15} are the same as the above -- it is -- D -CO-, -COO-, and -CO-NR^{24}- (here, R^{24} should become together with a hydrogen atom, a low-grade alkyl group, or a nitrogen atom in which R^{24} and R^{22} adjoin) [Chemical formula 10]



it may form (here, W, R^{12}, and m are the same as the above) -CS-, -CS-O-, and -CS-NR^{24}- (here, R^{24} is the same as the above), [Chemical formula 11]



(Here, R^{25} is a hydrogen atom, a low-grade alkyl group, or a cyano group), -}; or -SO_2-R^{26} (among a formula) which is SO_2- or a single bond R^{26} is a low-grade alkyl group, a lower alkylamino group, or a JI lower alkylamino group -- it is --;R^6, they are a hydrogen atom or a halogen atom -- R^7 -- a hydrogen atom, a low-grade alkyl group, or -$(CH_2)_q$-CO-R^{27} (the inside of a formula, and R^{27} -- a hydroxyl group, a lower alkoxy group, an aryloxy group, and an aralkyloxy group -- or) [Chemical formula 12]



it is (here, the same [W and m] as the above), and q is an integer of 1 thru/or 2 -- it is. A salt permitted on a carbo styryl compound shown by R^8 being a hydrogen atom, a halogen atom, a low-grade alkyl group, a hydroxyl group, a lower alkoxy group, a nitro group, an amino group, a carboxyl group, or a low-grade alkoxycarbonyl group], or its medicine manufacture.

[Claim 2]R^1, R^2, R^3, and R^8 are the same or different, and A hydrogen atom, A salt permitted on the carbo styryl compound according to claim 1 which is a halogen atom, nitro group, low-grade alkyl-group, and halo alkyl group, a lower alkoxy group, an amino group, a hydroxyl group, a carboxy group, or a low-grade alkoxycarbonyl group, or its medicine manufacture.

[Claim 3]A salt with which R^5 is permitted on the carbo styryl compound according to claim 2 which is a hydrogen atom, a low-grade alkyl group, a lower alkoxy group, or a halo alkyl group, or its medicine manufacture.

[Claim 4]A salt with which R^4 is permitted on the carbo styryl compound according to claim 3 which is -O-B-R^{13} (the inside of a formula, and B and R^{13} are the passages according to claim 1), or its medicine manufacture.

[Claim 5]A salt with which R^4 is permitted on the carbo styryl compound according to claim 3 which is -NR^{21}-D-R^{22} (the inside of a formula, R^{21}, R^{22}, and D are the passages according to

claim 1), or its medicine manufacture.
[Claim 6]A medicinal composition containing a salt permitted on the carbo styryl compound according to claim 1 to 5 or its medicine manufacture, and a carrier permitted in medicine.
[Claim 7]PDGF inhibitor which contains a salt permitted on the carbo styryl compound according to claim 1 to 5 or its medicine manufacture as an active principle.
[Claim 8]Smooth muscle growth inhibition medicine which contains a salt permitted on the carbo styryl compound according to claim 1 to 5 or its medicine manufacture as an active principle.
[Claim 9]A restenosis remedy which contains a salt permitted on the carbo styryl compound according to claim 1 to 5 or its medicine manufacture as an active principle.
[Claim 10]A nephritis remedy which contains a salt permitted on the carbo styryl compound according to claim 1 to 5 or its medicine manufacture as an active principle.

[Translation done.]

PRIOR ART

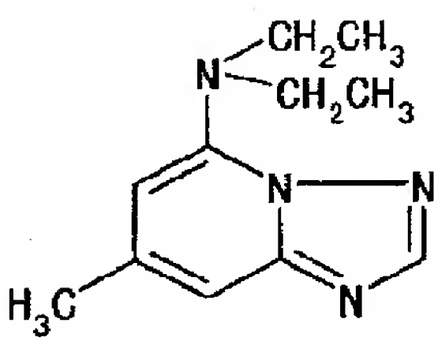
[0002]

[Description of the Prior Art]PDGF existed in blood platelets and was refined as a factor which has migration and growth stimulus activity mainly to a mesenchyme system cell. This protein forms a dimer and three kinds of isoforms, PDGF-AA, BB, and AB, exist from the combination of the A chain of molecular weight 12kDa, and the B chain of 18kDa. PDGF now A smooth muscle cell, a macrophage, endothelial cells besides blood platelets, Being secreted from fibrocyte is known and having achieved work important for the onsets and progress of various symptoms including arteriosclerosis besides a physiological phenomenon which are called the generating process and wound healing process of a living thing is known. For example, the chronic coronary-stenosis disease which makes arteriosclerosis the background of a cause of a disease, As a result of damaging intima by risk factor, such as hypertension and hyperlipidemia, blood platelets condense to a damaged area and cell growth factors, such as PDGF, are emitted to it, This draws monocyte and neutrophil leucocyte to a damaged area, and causing, when a vascular smooth muscle cell (media smooth muscle cell) and fibrocyte increase superfluously is known. In this arteriosclerosis lesion region, it is suggested by seeing the increase not only in PDGF but a PDGF receptor that PDGF is involving greatly as a vascular smooth muscle cell growth factor in arteriosclerosis.

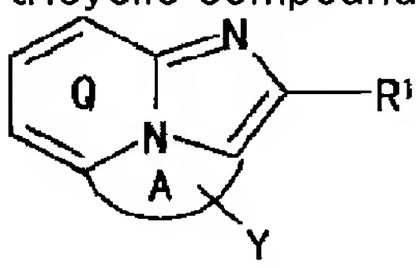
[0003]Although an endermic coronary vasodilatation way (PTCA) is the way method which progressed to urgency as a cure for ischemic heart disease in recent years, the problem is that the restenosis of coronary arteries happens in [postoperative] several months. As one of causes, when intima and a media expand and scrape, it is mentioned that receive damage, blood platelets condense to a damaged area, and chemotaxis growth factors, such as PDGF, are emitted. Happening [the migration to the intima of a media smooth muscle cell is caused by this, and / the restenosis of a blood vessel] idea ****.

[0004]PDGF is the most powerful growth factor to the mesangial cell of mesangium, and the role in various glomerular diseases is also large. Although the histologic characteristic which shows abolition of a glomerular function is glomerulosclerosis, this glomerulosclerosis is involving closely with the accumulation in a glomerulus of various extra-cellular matrices. Increasing of glomerular cells, especially a mesangial cell becomes important as a lesion preceded with these change. Although many growth factors and various factors including cytokine are participating in the growth reaction, PDGF bears the most important role also in them and mainly deriving growth of a mesangial cell and production of an extracellular matrix is known.

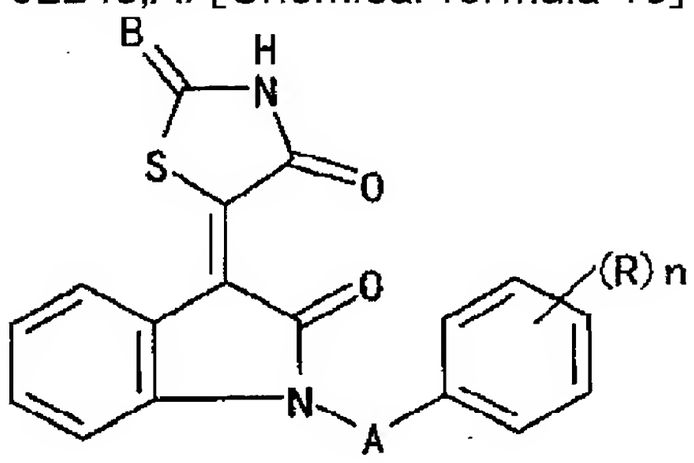
[0005]Thus, as a disease in which PDGF participates, arteriosclerosis, the restenosis, and a nephritis are mentioned, in addition diseases, such as chronic articular rheumatism, cancer, and hyperlipidemia, are known. Development of the remedy by checking PDGF according to each disease is furthered. For example, following TORAJIPIRU which has PDGF depressant action in JP,S57-38715,A [Chemical formula 13]



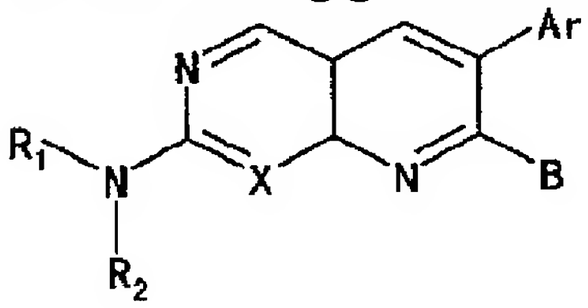
Blood vessel thickening depressant used as the main ingredients is indicated. The following tricyclic compound to JP,H8-81467,A. [Chemical formula 14]



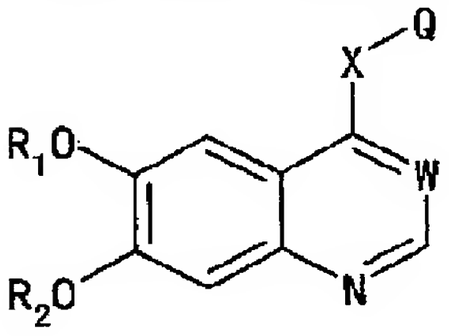
Having outstanding PDGF depressant action, antihypertensive effects, renal disease improving action, and hypolipidemic action is indicated. The following India linon derivative to JP,H8-92248,A. [Chemical formula 15]



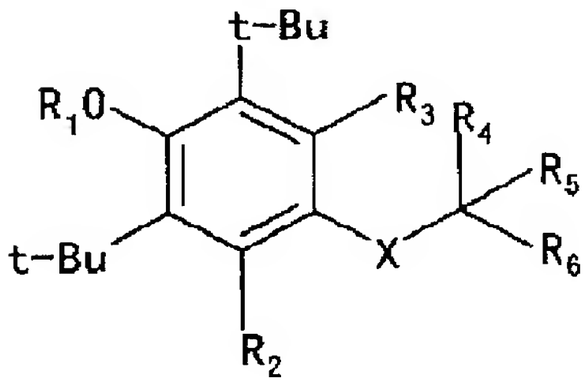
PDGF is checked selectively, for example, it is indicated that it is useful as prevention of ischemic heart disease by coronary angiography, such as acute myocardial infarction and angina pectoris, strangulation, and blockade, arteriosclerosis, an interstitial fibroid lung, osteoarthritis, chronic articular rheumatism, nephrosis, cancer, etc. and a remedy. In WO 96/No. 15128 gazette, it is a following general formula. [Chemical formula 16]



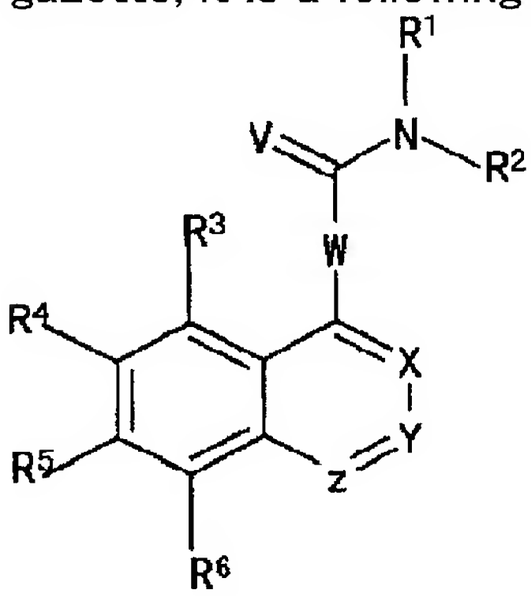
It is indicated that come out and the compound expressed has the depressant action of the restenosis. In WO 97/No. 17329 gazette, it is a following general formula. [Chemical formula 17]



It is indicated that come out and the quinoline derivative and quinazoline derivative which are shown have PDGF receptor self-phosphorylation inhibitory action. In JP,H9-188619,A, it is a following general formula. [Chemical formula 18]

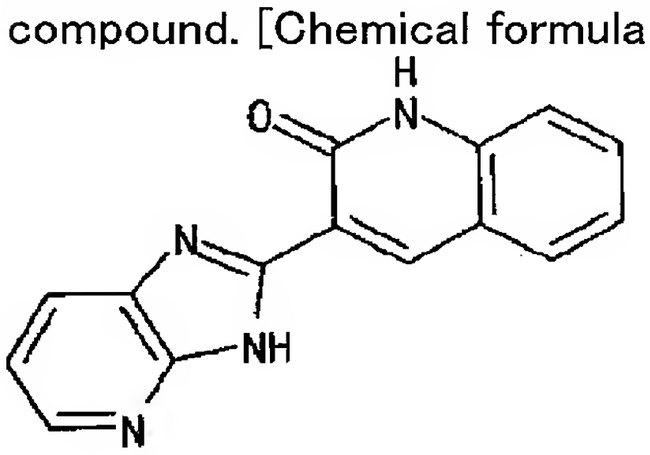


It comes out and it is shown that the compound expressed is useful as a blood vessel intima thickening depressant or a treating agent of the restenosis after PTCA. In WO 98/No. 14431 gazette, it is a following general formula. [Chemical formula 19]



When it comes out, and a compound shown checks phosphorylation of a PDGF receptor and checks unusual cell growth and migration, it is indicated that it is useful as prevention or a remedy of cell-growth nature diseases, such as arteriosclerosis, a blood vessel re-blockade disease, cancer, and glomerulosclerosis. However, a description which suggests there being not only no indication of a carbo styryl compound like the invention in this application checking PDGF in these advanced technology but it cannot be seen at all, either.

[0006]On the other hand as a compound which it has, carbo styryl structure JP,S59-176276,A (inhibition agent as a result of an antigen-antibody reaction), JP,S64-63518,A (antiarrhythmic drug), JP,H7-501313,A (alternative noncompetitive antagonist of a NMDA receptor), and JP,H8-508466,A (remedy of a psychosis) are indicated. Especially in JP,S63-230687,A, it is the following compound. [Chemical formula 20]



Although it ******, it differs from structure like the invention in this application of having Indore in the 3rd place of a carbostyryl skeleton. The use is a coronary-blood-flow increasing action etc., and completely differs from PDGF inhibitor which is a use of the invention in this application. Although development of remedies, such as arteriosclerosis, restenosis, or a nephritis, is furthered by checking PDGF now, it cannot yet be satisfied in activity. Therefore, there are an effect and activity more and development of outstanding PDGF inhibitor with high safety and easy directions for use was desired strongly.

[Translation done.]